IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Prior Apln Serial No.	:	09/079,758
Applicant	:	Dennis R. Morrison
Apln Filed	:	May 15, 1998
Art Unit	:	1617
Confirmation No.	:	8692
Examiner	:	Layla Soroush
Docket No.	:	MSC-22939-1
Customer No.	:	24957

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Declaration of Dennis R. Morrison, PhD Under 37 C.F.R. §1.132

1. I, Dennis R. Morrison, declare as follows, under penalty of perjury.

2. I hold a Bachelor of Science degree in Pharmacy awarded by the University of Florida in 1963, a Master of Science degree in Radiation Biophysics awarded by the University of Florida in 1966, and a Doctorate degree in Cellular and Molecular Biology awarded by the University of Florida in 1970.

3. From 1974 until 2006, I was employed as a Federal employee at the National Aeronautics and Space Administration (NASA), Johnson Space Center, Houston, Texas, where I have worked continually as a biomedical research scientist and senior laboratory manager, particularly in the fields of radiation and electromagnetic field effects on cells, biomedical imaging, cancer mechanisms, immunology, microencapsulation and drug delivery.

4. I have reviewed the Japanese patent (Patent No. JP 06-256728 A) to Hiroshi et al. (hereafter referred to as "**Hiroshi**"). I have reviewed the U.S. patent (Patent No. 5,039,558) to Sang et al.. I have reviewed the abstract in Cancer magazine to Sugarbaker et al. I have reviewed the German patent (Patent No. DE 19606804 A1) to Jund and Borrmann (hereafter referred to as "**Borrmann**").

Hiroshi's microcapsules do not contain encapsulated trigger particles. Further, as will be discussed later, the ability to encapsulate trigger particles in a microcapsule was not generally known in the art at the time of filing this patent application.

5. I have reviewed the Office action in U.S. Patent Application Serial No. 09/079,758, mailed June 14, 2007.

6. I offer the following comments on this issue:

6a. Unpredictable Results. We (myself and my fellow inventor) recognized that existing methods and techniques did not include the use of energy absorbing trigger particles in combination with an external energy source to melt an outer polymer membrane of a microcapsule for burst release purposes. Although we anticipated that the use of magnetic particles provided for an effective method of burst releasing the contents of a microcapsule, we anticipated that heating numerous magnetic particles to a temperature high enough to effectively melt an outer polymer membrane of a microcapsule would probably result in extensive damage to surrounding tissue. Specifically, the release of numerous heated magnetic particles into surrounding tissue predictably would cause widespread tissue damage. In the subject patent application, we described how temperatures between 41 - 43° C result in hyperthermia conditions (ref: page 4, paragraph [007] in the subject patent application). However, our experimentation resulted in the effective use of magnetic particles with a Curie point about 48° C (ref: FIG 2 in the subject patent application). We have determined that the use of magnetic particles from about 41 - 44° C or even up to as high as about 50° C would not cause widespread damage to neighboring cells due to local thermal effects (ref: page 8, paragraph [0018]). We have theorized that this unpredictable result is due to magnetic particles acting as a series of point heat sources with limited local thermal conduction outside of the microcapsules as opposed

opposed to creating a broad tissue hyperthermia condition. This unpredictable result is extendable to other energy absorbing trigger particles as described in the subject patent application's specification. And therefore, the application of the subject technology is extendable to a wide range of therapies.

6b. Long Felt Need. Since the 1980s, there has been a need for a better *in vivo* targeted release technique for encapsulated contents in a microcapsule. However, before the priority date of the subject application, there hasn't been a disclosure of the use of an external energy source in combination with energy absorbing trigger particles to melt an outer polymer membrane of a microcapsule. In short, with the exception of the technology described in the subject application, there is no technique, commercially available or otherwise, that provides burst release of microcapsules through the use of an external energy source in combination with energy absorbing trigger particles to melt an outer polymer membrane of a microcapsule.

6c. Attempts by Those Skilled in the Art to fill the Unsatisfied Need. Pages 3 - 7 of the subject application objectively list multiple attempts by those skilled in the art of conventional liposome or microcapsule delivery systems. All of these examples fail from the standpoint of the use of an external energy source in combination with energy absorbing trigger particles to melt an outer polymer membrane of a microcapsule. Further, in my expert opinion, the **Borrmann** reference does not fill this unsatisfied need. First, **Borrmann** discloses the use of a "ring of magnetic particles" encapsulated in a microsphere. Once exposed to a magnetic field, the ring becomes a thorn-like linear change. However, **Borrmann** does not disclose how he manufactures this "ring of magnetic particles" and encapsulates it in a microsphere. **Borrmann** contains no experimentation data. I have over 50 years of experience in chemistry and over 45 years in manufacturing microspheres as well as applications of microspheres. I can honestly say that it is beyond my skill to manufacture a micron-sized or submicron-sized "ring of magnetic particles" and subsequently encapsulate this ring in a microsphere, while maintaining the ring structure. Further, our (i.e., Dr. Morrison and myself) initial attempts to manufacture energy absorbing trigger particles encapsulated in microcapsules or "externally-tiggered (E-T) microcapsules" on Earth were unsuccessful. The first E-T microcapsules that we successfully manufactured occurred during space experiments on board the Space Shuttle, where

microgravity conditions allowed us to encapsulate the dense trigger particles as a suspension in the aqueous liquid phase, without sedimentation to the polymer interface where the outer membrane was being formed. In other words, during the manufacturing process, we had to learn how to keep the trigger particles separate from the polymer outer membrane. On Earth, due to a 1-g environment, the hydrophobic surface of the ceramic coated particles would be entrapped in the polymer outer membrane as it formed and would not be freely suspended in the internal liquid phase immediately next to the polymer outer membrane. Only after several microgravity experiments, as disclosed in the subject patent application, did we learn how to control certain environmental conditions to allow the formation of the claimed special microcapsules. We were able to apply the "lessons learned" from our experimentation on-board the Space Shuttle in the design of a unique microencapsulation manufacturing system (ref: U.S. Patent No. 7,094,045) to overcome the entrapment issue described above. In short, I believe **Borrmann** represents a non-enabling, prophetic reference and fails to satisfy the need for an effective microcapsule burst release technology.

6d. Acquiescence by Industry to the Patent Application's Validity by Honoring the Application through taking a License. The subject technology has been commercially licensed on a partially exclusive basis to Critical Care Innovations, Inc., a corporation of the State of Virginia, under NASA License Number DE-350; and Instrumentation Technology Associates, Inc., a corporation of the State of Pennsylvania, under NASA License Number DE-377. Both Critical Care Innovations and Instrumentation Technology Associates are actively working to bring the subject technology to actual clinical application.

Respectfully submitted,

Dennis R. Morrison, PhD